

10/511452

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FILE 'HOME' ENTERED AT 08:39:33 ON 06 NOV 2006

=> file ca

=> s prodrug? and (simple ester)

15300 PRODRUG?

539852 SIMPLE

580195 ESTER

79 SIMPLE ESTER

(SIMPLE(W)ESTER)

L1 1 PRODRUG? AND (SIMPLE ESTER)

=> d ibib abs

L1 ANSWER 1 OF 1 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 132:302814 CA

TITLE: Orally active peptidomimetic RGD analogs that are glycoprotein IIb/IIIa antagonists

AUTHOR(S): Wang, W.; Borchardt, R. T.; Wang, B.

CORPORATE SOURCE: Department of Chemistry, North Carolina State University, Raleigh, NC, 27695, USA

SOURCE: Current Medicinal Chemistry (2000), 7(4), 437-453  
CODEN: CMCHE7; ISSN: 0929-8673

PUBLISHER: Bentham Science Publishers

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 112 refs. Peptidomimetic RGD (Arg-Gly-Asp) analogs, which bind to glycoprotein (GP) IIb/IIIa on the surface of activated platelets, have been shown to inhibit platelet aggregation. Consequently, such RGD analogs can be used for the treatment of unstable angina pectoris and myocardial infarction. However, the low oral bioavailability for this class of compds. has been hindering their clin. development. Although many factors affect the oral activity of a drug, the limited membrane permeability of RGD analogs due to charge and high polarity is thought to be a major factor leading to the low oral activity of such compds. Another factor is the metabolic lability of some such RGD analogs in the presence of proteases and peptidases. During the last 5 yr, major progress has been made in the development of orally active RGD analogs. To improve the metabolic stability of RGD analogs, N-alkylation and C-terminal modification methods have been used successfully. To improve the membrane permeability of RGD analogs, two major strategies have been used. The first one is the strategy of prodrug. Along this line, simple ester prodrugs, double prodrugs, triple prodrugs, and cyclic prodrugs have been prepared with improved membrane permeability and oral activity. The second approach used is the de novo design of centrally constrained RGD analogs with improved oral bioavailability while maintaining the desired potency against GP IIb/IIIa. The lessons learned from the modification of RGD analogs could also help the future design of other peptidomimetic drugs with improved oral bioavailability.

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/511452

=> file ca

=> s alkyl ester prodrug?

571025 ALKYL

580195 ESTER

15300 PRODRUG?

L2 23 ALKYL ESTER PRODRUG?

(ALKYL(W) ESTER(W) PRODRUG?)

=> s l2 not l1

L3 23 L2 NOT L1

=> d ibib abs 1-23

L3 ANSWER 1 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 144:403722 CA  
TITLE: In vitro and in vivo evaluation of the metabolism and  
bioavailability of ester prodrugs of MGS0039  
(3-(3,4-dichlorobenzoyloxy)-2-amino-6-  
fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid), a  
potent metabotropic glutamate receptor antagonist  
AUTHOR(S): Nakamura, Masato; Kawakita, Yasunori; Yasuhara, Akito;  
Fukasawa, Yoshiki; Yoshida, Koji; Sakagami, Kazunari;  
Nakazato, Atsuro  
CORPORATE SOURCE: Medical Development Research Laboratories, Taisho  
Pharmaceutical Co., Ltd., Saitama, Japan  
SOURCE: Drug Metabolism and Disposition (2006), 34(3), 369-374  
CODEN: DMDSAI; ISSN: 0090-9556  
PUBLISHER: American Society for Pharmacology and Experimental  
Therapeutics  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB MGS0039 (3-(3,4-dichlorobenzoyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-  
2,6-dicarboxylic acid) has been identified as a potent and selective  
antagonist for metabotropic glutamate receptors. However, the oral  
bioavailability of MGS0039 is 10.9% in rats, due to low absorption.  
Several prodrugs, synthesized to improve absorption, exhibited 40 to 70%  
bioavailability in rats. This study investigated in vitro metabolism using  
liver S9 fractions from both cynomolgus monkeys and humans and oral  
bioavailability in cynomolgus monkeys to select the prodrug most likely to  
exhibit optimal pharmacokinetic profiles in humans. In monkeys,  
transformation to active substance was observed (5.9 - 72.8%) in liver S9  
fractions, and Bu, n-pentyl, 3-methylbutyl, and 4-methylpentyl ester  
prodrugs exhibited high transformation ratios (>64%). Cmax levels and F  
values after oral dosing increased to 4.1- to 6.3-fold and 2.4- to  
6.3-fold, resp., and a close relationship between transformation ratios  
and Cmax and F values was observed, indicating that the hydrolysis rate in  
liver S9 fractions is the key factor in determining oral bioavailability in  
monkeys. In humans, n-hexyl, n-heptyl, n-octyl, 5-methylbutyl, and  
6-methylpentyl ester prodrugs exhibited high transformation ratios (>65%)  
in liver S9 fractions. With these prodrugs, n-hexyl, n-heptyl, and  
5-methylpentyl ester, almost complete recovery (96 - 99%) was obtained.  
Given the transformation ratio, we anticipated that the n-heptyl  
alkyl ester prodrug would exhibit the highest  
oral bioavailability of active substances in humans, if the hydrolysis  
rate in liver S9 fractions is indeed the key factor in determining oral  
bioavailability in humans. On this basis, MGS0210 (3-(3,4-  
dichlorobenzoyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic  
acid n-heptyl ester) seems to be a promising candidate among MGS0039  
prodrugs.  
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/511452

L3 ANSWER 2 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 143:311659 CA  
TITLE: Bioconversion of naltrexone and its 3-O-alkyl  
-ester prodrugs in a human skin  
equivalent  
AUTHOR(S): Hammell, Dana C.; Stolarczyk, Elzbieta I.; Klausner,  
Mitch; Hamad, Mohamed O.; Crooks, Peter A.;  
Stinchcomb, Audra L.  
CORPORATE SOURCE: Department of Pharmaceutical Sciences, College of  
Pharmacy, University of Kentucky, Lexington, KY,  
40536-0082, USA  
SOURCE: Journal of Pharmaceutical Sciences (2005), 94(4),  
828-836  
CODEN: JPMSAE; ISSN: 0022-3549  
PUBLISHER: Wiley-Liss, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB The purpose of this study was to compare the percutaneous absorption and  
bioconversion of naltrexone (NTX), naltrexone-3-O-valerate (VAL), and  
naltrexone-3-O-(2'-ethylbutyrate) (ETBUT) in a human skin equivalent model  
(EpiDerm) and in fresh human skin in vitro. NTX diffusion and metabolism to  
6- $\beta$ -naltrexol (NTXol) were quantitated and compared in the EpiDerm  
and in excised fresh human skin. VAL and ETBUT diffusion and  
bioconversion studies were also completed in EpiDerm. Naltrexone  
bioconverted to levels of 3 $\pm$ 2% NTXol in the EpiDerm and 1 $\pm$ 0.5% in  
fresh human skin. VAL hydrolyzed rapidly in the EpiDerm and mainly  
(93 $\pm$ 4%) NTX was found in the receiver compartment, similar to human  
skin. More intact ETBUT permeated the EpiDerm tissue compared to VAL, and  
only 15 $\pm$ 11% NTX was found in the receiver. Significantly higher fluxes  
of NTX and the prodrugs were observed with the EpiDerm compared to human  
skin. A similar flux enhancement level was observed for VAL, compared to NTX  
base, in the EpiDerm and the human skin. Metabolically active human  
epidermal models like EpiDerm are useful as an alternative exptl. system  
to human skin for prediction of topical/transdermal drug/prodrug  
bioconversion.  
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 143:102963 CA  
TITLE: In vivo evaluation of 3-O-alkyl ester transdermal  
prodrugs of naltrexone in hairless guinea pigs  
AUTHOR(S): Valiveti, Satyanarayana; Hammell, Dana C.; Paudel,  
Kalpana S.; Hamad, Mohamed O.; Crooks, Peter A.;  
Stinchcomb, Audra L.  
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of  
Kentucky College of Pharmacy, Lexington, KY,  
40536-0082, USA  
SOURCE: Journal of Controlled Release (2005), 102(2), 509-520  
CODEN: JCREEC; ISSN: 0168-3659  
PUBLISHER: Elsevier B.V.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Naltrexone (NTX) is a potent competitive antagonist with high affinity for  
the  $\mu$ -opioid receptor. Therapeutically, NTX is used for the treatment  
of alc. dependence and opioid addiction; however, it does not have the  
ideal physicochem. properties necessary to achieve therapeutic plasma  
concns. via the transdermal route. The aim of the present investigation  
was to evaluate the in vivo transdermal delivery of three 3-O-  
alkyl ester prodrugs of NTX, including  
NTX-3-O-acetate (ACE-NTX), NTX-3-O-propionate (PROP-NTX), and  
NTX-3-O-hexanoate (HEX-NTX) in hairless guinea pigs. The pharmacokinetic  
parameters for NTX and the 3-O-alkyl ester  
prodrugs of NTX were determined after i.v. drug administration and  
topical drug application of transdermal therapeutic systems (TTS) in  
guinea pigs. The results of the in vivo studies showed mean steady-state  
plasma concns. of NTX from NTX, ACE-NTX, PROP-NTX and HEX-NTX at 4.2,  
25.2, 16.0, and 8.3 ng/mL, resp. These NTX plasma concns. were maintained  
for 48 h. The results of these in vivo studies demonstrated that ACE-NTX  
and PROP-NTX prodrugs of NTX were the most promising drug candidates for  
transdermal delivery.  
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/511452

L3 ANSWER 4 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 139:386133 CA  
TITLE: Synthesis and evaluation of ketorolac ester prodrugs  
for transdermal delivery  
AUTHOR(S): Doh, Hea-Jeong; Cho, Won-Jea; Yong, Chul-Soon; Choi,  
Han-Gon; Kim, Jung Sun; Lee, Chi-Ho; Kim, Dae-Duk  
CORPORATE SOURCE: College of Pharmacy, Pusan National University, Pusan,  
609-735, S. Korea  
SOURCE: Journal of Pharmaceutical Sciences (2003), 92(5),  
1008-1017  
CODEN: JPMSAE; ISSN: 0022-3549  
PUBLISHER: Wiley-Liss, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Alkyl esters of ketorolac were synthesized as potential prodrugs for transdermal delivery and evaluated to determine the relationship between their skin permeation characteristics and their physicochem. properties. Solubility of the prodrugs in various vehicles was determined at room temperature while lipophilicity was obtained as 1-octanol/water partition coeffs. (logP) and capacity factors (k') using HPLC. Metabolism of the prodrugs to ketorolac was studied both in rat skin homogenate and in plasma. Rat skin permeation characteristics of the prodrugs saturated in propylene glycol were investigated using the Keshary-Chien permeation system at 37°. An increase in logP and capacity factor values of the prodrugs were observed in proportion to their alkyl chain length. Good linear relationship between the logP values and capacity factor was observed ( $r^2 = 0.92$ ). Prodrugs were rapidly degraded to ketorolac both in the skin homogenate and in plasma following a first-order kinetics. To determine accurate amts. of prodrug permeated, both the prodrug and parent drug concentration in the receptor solution

were determined in mole units. The skin permeation rate of the alkyl ester prodrugs was significantly higher with a shorter lag time than that of ketorolac. The permeation rate of ketorolac reached maximum in its 1-Pr ester form as 46.61 nmol/cm<sup>2</sup>/h, and a parabolic relationship was observed between the permeation rate and the logP values of the prodrugs. Alkyl ester prodrugs of ketorolac having optimum lipophilicity could improve the transdermal delivery of ketorolac.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 139:106262 CA  
TITLE: Straight-chain naltrexone ester prodrugs: diffusion  
and concurrent esterase biotransformation in human  
skin  
AUTHOR(S): Stinchcomb, Audra L.; Swaan, Peter W.; Ekabo, Opinya;  
Harris, Kathleen K.; Browe, Jennifer; Hammell, Dana  
C.; Cooperman, Todd A.; Pearsall, Michael  
CORPORATE SOURCE: Division of Pharmaceutical Sciences, College of  
Pharmacy, University of Kentucky, Lexington, KY,  
40536-0082, USA  
SOURCE: Journal of Pharmaceutical Sciences (2002), 91(12),  
2571-2578  
CODEN: JPMSAE; ISSN: 0022-3549  
PUBLISHER: Wiley-Liss, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Naltrexone (NTX) is an opioid antagonist used for treatment of narcotic  
dependence and alcoholism. Transdermal naltrexone delivery is desirable  
to help improve patient compliance. The purpose of this study was to  
increase the delivery rate of NTX across human skin by using lipophilic  
alkyl ester prodrugs. Straight-chain  
naltrexone-3-alkyl ester prodrugs of 2-7  
carbons in chain length were synthesized and evaluated. In vitro human  
skin permeation rates were measured using a flow-through diffusion cell  
system. The m.p.s., solubilities, and skin disposition of the drugs were  
determined. The prodrugs were almost completely hydrolyzed on passing through  
the skin and appeared as NTX in the receiver compartment. The mean NTX  
flux from the prodrug-saturated solns. exceeded the flux of NTX base by  
.apprx.2-7-fold. The amount of drug detected in the skin was significantly  
greater after treatment with the prodrug solns. compared with treatment  
with NTX base. The extent of parent drug (NTX) regeneration in the intact  
skin ranged from 28 to 91%. Higher NTX regeneration percentages in skin  
appeared to correlate with increased drug delivery rates. Definitively,  
the highly oil-soluble prodrugs provide a higher NTX flux across human skin  
in vitro and undergo significant metabolic conversion in the skin.  
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L3 ANSWER 6 OF 23 CA COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 138:343674 CA  
 TITLE: Rat skin permeation of diclofenac and its prodrugs  
 AUTHOR(S): Doh, Hea-Jeong; Cho, Won-Jea; Yong, Chul-Soon; Lee, Chi-Ho; Kim, Dae-Duk  
 CORPORATE SOURCE: College of Pharmacy, Pusan National University, Pusan, 609-735, S. Korea  
 SOURCE: Yakche Hakhoechi (2001), 31(2), 95-100  
 CODEN: YAHAEX; ISSN: 0259-2347  
 PUBLISHER: Korean Society of Pharmaceutics  
 DOCUMENT TYPE: Journal  
 LANGUAGE: Korean  
 AB Various alkyl ester prodrugs of diclofenac were synthesized in order to investigate the relationship between their skin permeation characteristics and physicochem. properties. Solubility in various vehicles was measured at room temperature 1-Octanol/water partition coeffs. (Log P) and capacity factors (k') were measured to determine the lipophilicity of the prodrugs. Stability of prodrugs in the skin extract and homogenate was also investigated before conducting the skin permeation studies. Increases in the Log P and capacity factor values were observed when alkyl esters of diclofenac were prepared Since the aqueous solubility of the prodrugs was not high enough, they were saturated in propylene glycol (PG) for skin permeation studies. Prodrugs were rapidly metabolized to diclofenac, both in skin homogenate and in dermal extract of skin. The skin permeation rate of alkyl ester prodrugs was significantly higher than diclofenac with shorter lag time. Moreover, a parabolic relationship was observed between the permeation rate and the log P values of prodrugs, and the maximum flux was achieved at a log P value of around 4.0.

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L3 ANSWER 7 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 136:42724 CA  
TITLE: Alkyl ester prodrugs for  
improved topical delivery of ibuprofen  
AUTHOR(S): Bansal, Arvind K.; Khar, R. K.; Dubey, R.; Sharma, A.  
K.  
CORPORATE SOURCE: College of Pharmacy, New Delhi, 110 017, India  
SOURCE: Indian Journal of Experimental Biology (2001), 39(3),  
280-283  
CODEN: IJEBA6; ISSN: 0019-5189  
PUBLISHER: National Institute of Science Communication, CSIR  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Topical delivery of ibuprofen directly to the site of inflammation can  
overcome gastrointestinal side effects associated with its long term oral  
administration. The set of physicochem. properties necessary for optimum  
topical delivery of ibuprofen can be imparted by formation of its ester  
prodrugs. Various alkyl ester prodrugs (Me,  
Et, Pr, iso-Pr, Bu, iso-Bu, sec-Bu, tert-Bu, n-pentyl, hexyl, heptyl,  
octyl, lauryl, cetyl and octadecyl esters) were synthesized and studied  
for their physicochem. properties and activity in the carrageenan induced  
rat paw edema by topical route. Favorable shift in lipophilicity and self  
penetration enhancing effect of prodrugs responded in improved topical  
activity over the parent drug ibuprofen.  
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 23 CA COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 134:21374 CA  
 TITLE: Enhancement of the systemic and CNS specific delivery  
 of L-dopa by the nasal administration of its water  
 soluble prodrugs  
 AUTHOR(S): Kao, Huaihung Danny; Traboulsi, Ashraf; Itoh, Soichi;  
 Dittert, Lewis; Hussain, Anwar  
 CORPORATE SOURCE: Endo Pharmaceuticals, Garden City, NY, 11530, USA  
 SOURCE: Pharmaceutical Research (2000), 17(8), 978-984  
 CODEN: PHREEB; ISSN: 0724-8741  
 PUBLISHER: Kluwer Academic/Plenum Publishers  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The present study was conducted to evaluate the utility of the nasal route  
 for the systemic delivery of L-dopa using water soluble prodrugs of L-dopa  
 and to examine if this delivery method will result in preferential  
 delivery to the CNS. Several alkyl ester  
 prodrugs of L-dopa were prepared and their physicochem. properties  
 were determined. In vitro hydrolysis rate consts. in buffer, rat plasma, rat  
 brain homogenate, rat CSF, and rat nasal perfusate were determined by HPLC. In  
 vivo nasal expts. were carried out in rats. Levels of L-dopa and dopamine  
 in plasma, CSF, and olfactory bulb were determined using HPLC method with  
 electrochem. detection. All the prodrugs showed improved solubility and  
 lipophilicity with relatively fast in vitro conversion in rat plasma.  
 Absorption was fast following nasal delivery of the prodrugs with  
 bioavailability around 90%. Dopamine plasma levels did not change  
 significantly following nasal administration of the Bu ester prodrug.  
 Olfactory bulb and CSF L-dopa concentration were higher following nasal  
 delivery  
 of the Bu ester prodrug compared to an equivalent i.v. dose. Utilization of  
 water soluble prodrugs of L-dopa via the nasal route in the treatment of  
 Parkinson's disease may have therapeutic advantages such as improved  
 bioavailability, decreased side effects, and potentially enhanced CNS  
 delivery.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 23 CA COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 126:122360 CA  
 TITLE: Synthesis and evaluation of 5' alkyl  
 ester prodrugs of zidovudine for  
 directed lymphatic delivery  
 AUTHOR(S): Bibby, David C.; Charman, William N.; A. Charman,  
 Susan; Iskander, Magdy N.; Porter, Christopher J. H.  
 CORPORATE SOURCE: Department of Pharmaceutics, Victorian College of  
 Pharmacy, Monash University (Parkville Campus), 381  
 Royal Pde, Parkville, Victoria, 3052, Australia  
 SOURCE: International Journal of Pharmaceutics (1996), 144(1),  
 61-70  
 CODEN: IJPHDE; ISSN: 0378-5173  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The butanoic, lauric, and oleic acid ester prodrugs of the anti-AIDS drug  
 zidovudine (AZT) have been synthesized and assessed for their ability to  
 promote the transport of AZT through the intestinal lymph (a major  
 reservoir for the human immunodeficiency virus (HIV)). The octanol/water  
 partition co-efficient and triglyceride solubility of the AZT prodrugs  
 increased with increasing chain length of the alkyl pro-moiety, and the  
 observed values were consistent with that required for potential intestinal  
 lymphatic transport after oral administration. The intestinal lymphatic  
 transport of AZT and the ester prodrugs was assessed after intraduodenal  
 administration as a micellar lipid solution in an anesthetized rat model.  
 Systemic blood was also sampled in order to estimate the overall extent of  
 absorption. The lymphatic transport of AZT was similar when administered as  
 either AZT alone or the lipophilic ester prodrugs, where the amount of AZT  
 collected in fistulated mesenteric lymph was approx. 0.1-0.2% of the  
 administered dose (15 mg/kg AZT). The extent of absorption of AZT, estimated  
 from the area under the plasma concentration time profiles of AZT, when dosed

as

either parent compound or the lipophilic esters, was essentially complete.  
 These data suggest that rapid bioconversion of the ester prodrugs to AZT  
 in either the intestinal lumen or the enterocyte limits exploitation of  
 this approach as a means of enhancing the selective lymphatic delivery of  
 AZT.

L3 ANSWER 10 OF 23 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 125:316126 CA

TITLE: Permeation of buprenorphine and its 3-alkyl-  
ester prodrugs through human skinAUTHOR(S): Stinchcomb, Audra L.; Paliwal, Anupam; Dua, Rajesh;  
Imoto, Hirofumi; Woodard, Ronald W.; Flynn, Gordon L.CORPORATE SOURCE: College Pharmacy, University Michigan, Ann Arbor, MI,  
48109, USA

SOURCE: Pharmaceutical Research (1996), 13(10), 1519-1523

CODEN: PHREEB; ISSN: 0724-8741

PUBLISHER: Plenum

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Homologous 3-alkyl-ester prodrugs (C2 to C4)

of buprenorphine with decreased crystallinity have been synthesized and evaluated for transdermal delivery commensurate with opioid dependence treatment. To assess the influence of derivatization on delivery, the permeation of the prodrugs through human skin was determined in vitro. Prodrug metabolism was measured in human blood and skin supernatant in vitro along with chemical hydrolysis controls. The prodrugs' octanol/water partition coeffs. were measured. Without exception, the prodrugs were completely hydrolyzed on passing through the skin and appeared as buprenorphine in the receptor compartment. However, using saturation conditions, in no instance did the buprenorphine flux through skin from a prodrug solution exceed the flux of buprenorphine base itself in vitro. Moreover, the flux of the acetyl ester, the least hydrophobic of the prodrugs, was not significantly elevated upon stripping the skin. Whether in blood or the skin supernatant, the prodrugs hydrolyzed in an apparent first-order fashion and rate consts. and half-lives were calculated. We conclude from the results that the prodrugs' very high octanol/water partition coeffs. (hydrophobicity) placed them in viable tissue layer controlled diffusion. Moreover, the flux of the acetyl ester, the least hydrophobic of the prodrugs, was not significantly elevated upon stripping the skin. Whether in blood or the skin supernatant, the prodrugs hydrolyzed in an apparent first-order fashion and rate consts. and half-lives were calculated. We conclude from the results that the prodrugs' very high octanol/water partition coeffs. (hydrophobicity) placed them in viable tissue layer controlled diffusion. Consequently, one does not derived the potential flux-increasing benefit of reducing crystallinity that was expected.

L3 ANSWER 11 OF 23 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 124:211800 CA

TITLE: Transdermal prodrug concepts: permeation of buprenorphine and its alkyl esters through hairless mouse skin and influence of vehicles

AUTHOR(S): Imoto, Hirofumi; Zhou, ZiQi; Stinchcomb, Audra L.; Flynn, Gordon L.

CORPORATE SOURCE: Coll. Pharmacy, Univ. Michigan, Ann Arbor, MI, 48109-1065, USA

SOURCE: Biological &amp; Pharmaceutical Bulletin (1996), 19(2), 263-7

CODEN: BPBLEO; ISSN: 0918-6158

PUBLISHER: Pharmaceutical Society of Japan

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In vitro skin permeation of buprenorphine (BUP) and three of its alkyl ester prodrugs was evaluated using hairless mouse skin. The 3 esters selected were the acetyl ester (Ac-BUP), Bu ester (Bu-BUP), and iso-Bu ester (Isb-BUP). These drugs were applied on the skin as saturated slurries in 3 vehicles commonly used to formulate agents for transdermal purposes: propylene glycol, polyethylene glycol 400 (PEG 400), and light mineral oil. Unique solubilities were found for each drug on each vehicle. Fluxes through hairless mouse skin were evaluated for each combination of drug and vehicle using Franz diffusion cells. From PEG 400 formulations, the skin fluxes of BUP, Ac-BUP, Bu-BUP, and Isb-BUP were 0.47, 1.64, 0.33, 0.75  $\mu\text{g}/\text{cm}^2/\text{h}$ , resp. Thus, among the 3 potential prodrugs chosen, only Ac-BUP showed significantly higher skin fluxes than BUP. There were no inter-vehicle differences in the fluxes from saturated slurries between the vehicles. Moreover, all the esters were detected substantially in the form of regenerated parent drug (BUP) in the receptor compartment. Indeed, only Ac-BUP exited the skin in a measurably intact form, but the fraction escaping metabolism in transit was small (approx. 2%). However, based on drug dispositions in the skin, the regeneration of buprenorphine seems to depend on the alkyl chain length of the ester moiety. The molar percentages of regenerated parent drug in whole drug collected from the skin following the permeation expts. were: Ac-BUP, 9.2%; Bu-BUP, 40.7%; Isb-BUP, 9.6%, resp. Thus, only Ac-BUP appears promising as a prodrug of buprenorphine, because it is not overly hydrophilic for skin permeation and is also highly metabolized to the parent compound while in the skin.

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L3 ANSWER 12 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 123:350110 CA  
TITLE: Transdermal delivery of buprenorphine 3-alkyl  
-ester prodrugs for treatment of  
opioid dependence  
AUTHOR(S): Stinchcomb, Audra Lynn  
CORPORATE SOURCE: Univ. of Michigan, Ann Arbor, MI, USA  
SOURCE: (1995) 127 pp. Avail.: Univ. Microfilms Int., Order  
No. DA9527747  
From: Diss. Abstr. Int., B 1995, 56(4), 2034  
DOCUMENT TYPE: Dissertation  
LANGUAGE: English  
AB Unavailable

10/511452

L3 ANSWER 13 OF 23 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 121:117540 CA

TITLE: Effect of group substitution on the physicochemical properties of ibuprofen prodrugs

AUTHOR(S): Bansal, Arvind K.; Khar, R. K.; Dubey, R.; Sharma, A. K.

CORPORATE SOURCE: Coll. Pharm., New Delhi, India

SOURCE: Pharmazie (1994), 49(6), 422-4

CODEN: PHARAT; ISSN: 0031-7144

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of alkyl ester prodrugs of

ibuprofen was synthesized and studied for its physicochem. properties like aqueous solubility, octanol-water partition coefficient and hydrolysis kinetics in aqueous

buffer and human plasma. These physicochem. parameters have a forebearing on the overall activity profile of these prodrugs. Math. relationships have been derived to characterize these properties.



10/511452

L3 ANSWER 14 OF 23 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 121:26274 CA

TITLE: Quantitation of activity of alkyl ester prodrugs of ibuprofen

AUTHOR(S): Bansal, A. K.; Dubey, R.; Khar, R. K.

CORPORATE SOURCE: Coll. Pharm., Pushp Vihar, New Delhi, 110 017, India

SOURCE: Drug Development and Industrial Pharmacy (1994), 20(12), 2025-34

CODEN: DDIPD8; ISSN: 0363-9045

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A quant. relationship has been derived for the physicochem. properties and pharmacol. activity of alkyl ester prodrugs of ibuprofen. A comprehensive study consisting of aqueous solubility, octanol-water partition coefficient, hydrolysis kinetics in aqueous buffer (pH 7.4) & human plasma, ulcerogenic studies, anti-inflammatory and analgesic activity was carried on alkyl ester prodrugs of ibuprofen. Pr and Bu esters offered significant improvement in oral delivery of ibuprofen in terms of reduced gastroulcerogenicity and maintenance of pharmacol. activity.

10/511452

L3 ANSWER 15 OF 23 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 120:37994 CA

TITLE: Transport and degradation characteristics of methotrexate dialkyl ester prodrugs across tape-stripped hairless mouse skin

AUTHOR(S): Fort, James J.; Shao, Zezhi; Mitra, Ashim K.

CORPORATE SOURCE: Sch. Pharm. Pharmacal Sci., Purdue Univ., West Lafayette, IN, 47907, USA

SOURCE: International Journal of Pharmaceutics (1993), 100(1-3), 233-9

CODEN: IJPHDE; ISSN: 0378-5173

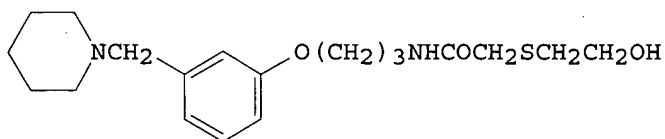
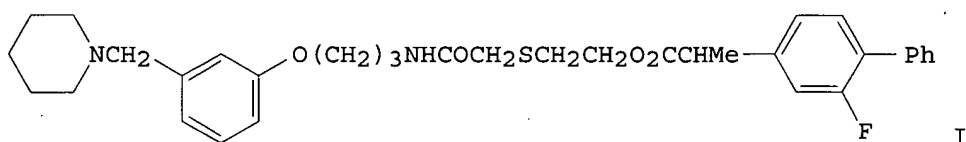
DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of methotrexate dialkyl esters were examined with respect to their permeability across tape-stripped hairless mouse skin. The dialkyl esters showed a parabolic permeability vs. side chain length relationship with the di-Me ester being the most permeable compound. These compounds were also found to undergo an increased degree of degradation with increased ester chain length during the diffusion process, while with substantially reduced degradation occurring with the branched chain diisopropyl ester. No measurable methotrexate was formed during the course of the experiment, apparently due to the chemical and enzymic stability of the intermediate  $\alpha$ - and  $\gamma$ -monoesters.

10/511452

L3 ANSWER 16 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 115:189560 CA  
TITLE: Design and in vivo evaluation of antiinflammatory  
flurbiprofen chimera drug to reduce gastric irritation  
AUTHOR(S): Imai, Teruko; Fukuhara, Akira; Otagiri, Masaki; Ueda,  
Ikuo  
CORPORATE SOURCE: Fac. Pharm. Sci., Kumamoto Univ., Kumamoto, 862, Japan  
SOURCE: Drug Delivery System (1991), 6(2), 83-7  
CODEN: DDSYEI; ISSN: 0913-5006  
DOCUMENT TYPE: Journal  
LANGUAGE: Japanese  
GI



AB The anti-inflammatory effect, gastrototoxicity, and in vivo absorption property of a chimera drug (I) of flurbiprofen (FP) with histamine H<sub>2</sub>-antagonist (II), were compared with those of FP and FP Me ester. I and FP Me ester were only slightly hydrolyzed in a pH 1.2-7.4 buffer in the absence or presence of pepsin and trypsin, in contrast to fast hydrolysis ( $t_{1/2}$  .apprx.20 s) in rat plasma. I inhibited carrageenin-induced paw swelling in the same level as FP alone and reduced gastrototoxicity in comparison to equivalent dose of FP, whereas the coadministration of FP with II did not affect gastrototoxicity of FP. FP Me ester caused slightly less damage to the gastric mucosa than FP alone. The plasma concentration of FP after administration of FP derivs. were similar to FP alone. These data suggested that the chimera drug is effective for reduction of gastric damage, compared with either FP or alkyl ester prodrug like Me ester.

L3 ANSWER 17 OF 23 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 115:78785 CA

TITLE: Role of enzymic lability in the corneal and conjunctival penetration of timolol ester prodrugs in the pigmented rabbit

AUTHOR(S): Chien, Du Shieng; Sasaki, Hitoshi; Bundgaard, Hans; Buur, Anders; Lee, Vincent H. L.

CORPORATE SOURCE: Sch. Pharm., Univ. South. California, Los Angeles, CA, 90033, USA

SOURCE: Pharmaceutical Research (1991), 8(6), 728-33

CODEN: PHREEB; ISSN: 0724-8741

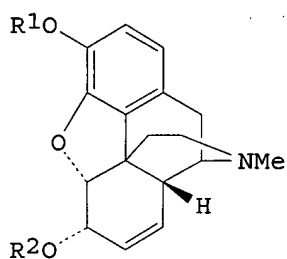
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The main objective of this study was to investigate how enzymic lability would affect the extent of corneal and conjunctival penetration of a series of alkyl, cycloalkyl, and aryl ester prodrugs of timolol in the pigmented rabbit. Enzymic lability of the prodrugs was studied in corneal epithelial and conjunctival homogenates, while their corneal and conjunctival penetration was determined using the isolated tissues in the modified Ussing chamber. The straight-chain alkyl and the unsubstituted cycloalkyl esters were hydrolyzed more rapidly than their corresponding branched chain and substituted analogs as well as the aryl esters. The corneal and conjunctival penetration of all prodrugs, regardless of enzymic lability, varied parabolically with lipophilicity. Moreover, the enzymically more labile straight-chain alkyl esters penetrated the cornea and the conjunctiva more readily than the more stable branched-chain esters of comparable lipophilicity. Enzymic lability is, therefore, an addnl. factor that should be considered in designing alkyl ester prodrugs with improved ocular drug delivery characteristics. Enzymic lability does not, however, play as important a role as lipophilicity in the corneal and conjunctival penetration of cycloalkyl and aryl ester prodrugs.

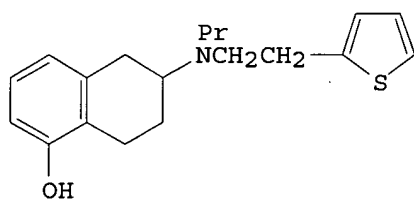
10/511452

L3 ANSWER 18 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 115:57028 CA  
TITLE: Utilization of prodrugs to enhance the transdermal  
absorption of morphine  
AUTHOR(S): Drustrup, Joern; Fullerton, Ann; Christrup, Lona;  
Bundgaard, Hans  
CORPORATE SOURCE: Dep. Pharm. Chem., R. Dan. Sch. Pharm., Copenhagen,  
DK-2100, Den.  
SOURCE: International Journal of Pharmaceutics (1991),  
71(1-2), 105-16  
CODEN: IJPHDE; ISSN: 0378-5173  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
GI



AB The feasibility of providing transdermal delivery of morphine was examined using the prodrug approach. Various alkyl esters (I, R1 and R2 = COEt, COCHMe2, H, eg.) formed at the 3- and/or 6-hydroxy group in morphine were prepared and their physicochem. and skin penetration properties studied as well as their hydrolysis kinetics. The esters showed generally a higher water and lipid solubility than morphine and were also much more lipophilic than the parent drug in terms of octanol-buffer partition coeffs. Diffusion expts. in vitro using human skin samples showed that whereas morphine did not penetrate the skin to any measurable extent whether applied in the form of saturated solns. in water at pH 7.0 or in iso-Pr myristate, the ester prodrugs showed a high penetrating capacity under the same conditions. Steady-state fluxes up to 35  $\mu\text{g}$  morphine/cm<sup>2</sup>/h were observed. For some esters essentially all of the amts. penetrated were presented in the receptor phase as morphine. The study demonstrates the feasibility of achieving transdermal delivery of morphine based on the ready conversion and the favorable skin penetration properties of morphine esters which in turn are attributed to their combination of adequate water solubility and lipophilicity.

L3 ANSWER 19 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 114:128899 CA  
TITLE: Transdermal administration of the dopamine agonist  
N-0437 and seven ester prodrugs: comparison with oral  
administration in the 6-OHDA turning model  
AUTHOR(S): Den Daas, Izaak; Tepper, Pieter G.; Rollema, Hans;  
Horn, Alan S.  
CORPORATE SOURCE: Univ. Cent. Pharm., State Univ. Groningen, Groningen,  
NL-9713 AW, Neth.  
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1990),  
342(6), 655-9  
CODEN: NSAPCC; ISSN: 0028-1298  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
GI



AB The potent and selective D2-agonist N-0437 (I) undergoes considerable first-pass metabolism after oral administration due to glucuronidation of the phenolic group. In an attempt to improve its bioavailability, seven ester prodrugs of I were synthesized, i.e. the acetyl-, propionyl-, isobutyryl-, pivaloyl-, 2-aminophenyl-, 2-methoxyphenyl- and 2,4-dimethylphenyl-analogs. In vivo activities were assessed by measuring contralateral turning after transdermal administration of I and its prodrugs to rats with unilateral 6-OHDA lesions of the nigrostriatal pathway. From time-effect curves the area under the curve for sep. time intervals was taken as a measure of dopaminergic activity during that interval. Slowly hydrolyzing prodrugs, which are known to show an improved duration of action after oral administration, are devoid of activity after transdermal application. The acetyl-, the propionyl- and the isobutyryl analogs, which are prodrugs with a relatively high hydrolysis rate, were found to have interesting and promising profiles following transdermal application.

L3 ANSWER 20 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 113:158551 CA  
TITLE: Prodrug approach of orotic acid using an absorption  
model  
AUTHOR(S): Fuerst, Walter; Neubert, Reinhard; Jurkschat, Thomas;  
Luecke, Lothar  
CORPORATE SOURCE: Sekt. Pharm., Martin-Luther-Univ., Halle-Wittenberg,  
DDR-4010, Ger. Dem. Rep.  
SOURCE: International Journal of Pharmaceutics (1990),  
61(1-2), 43-9  
CODEN: IJPHDE; ISSN: 0378-5173  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB A series of ester prodrugs of orotic acid were synthesized. Using in  
vitro methods, in particular, an absorption model system, the n-Bu ester  
of orotic acid was found to be the ester prodrug with optimal physicochem.  
properties. Pharmacokinetic studies on rabbits confirmed these results.  
The bioavailability of orotic acid after oral administration of the n-Bu  
ester prodrug was 3.4-times higher as compared to the methylglucamine salt  
or orotic acid. A similar increase in bioavailability was predicted based  
on the in vitro half life for transport in the absorption model.

10/511452

L3 ANSWER 21 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 112:42446 CA  
TITLE: Prodrugs of 5-iodo-2'-deoxyuridine for enhanced ocular transport  
AUTHOR(S): Narurkar, Milind M.; Mitra, Ashim K.  
CORPORATE SOURCE: Sch. Pharm. Pharm. Sci., Purdue Univ., West Lafayette, IN, 47907, USA  
SOURCE: Pharmaceutical Research (1989), 6(10), 887-91  
CODEN: PHREEB; ISSN: 0724-8741  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Problems associated with the use of 5-iodo-2'-deoxyuridine (IDU) in the treatment of herpes simplex keratitis can be attributed largely to the polar nature of IDU resulting in its poor permeability across the lipoidal epithelial layer of the corneal membrane. Five aliphatic 5'-esters of IDU were synthesized and evaluated as prodrugs for potential use in the treatment of deep ocular infections such as stromal keratitis, iritis, and even retinitis. A parabolic relationship between in vitro corneal membrane permeability and carbon chain length of prodrugs is evident. For a given prodrug, enzymic hydrolysis proceeded most readily in iris-ciliary body, followed by cornea and aqueous humor. An increase in carbon chain length made the prodrugs more enzymically labile but more resistant to chemical hydrolysis at pH 7.4 and 34°. The 5'-butyryl ester of IDU exhibited an approx. fourfold increase in aqueous humor IDU concentration relative to IDU at 25 min following instillation of 25- $\mu$ L 5 mM solns.



L3 ANSWER 22 OF 23 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 111:84015 CA

TITLE: Short-chain alkyl esters of L-dopa as prodrugs for rectal absorption

AUTHOR(S): Fix, Joseph A.; Alexander, Jose; Cortese, Margot; Engle, Karen; Leppert, Paula; Repta, Arnold J.

CORPORATE SOURCE: INTERx Res. Corp., Lawrence, KS, 66046, USA

SOURCE: Pharmaceutical Research (1989), 6(6), 501-5

CODEN: PHREEB; ISSN: 0724-8741

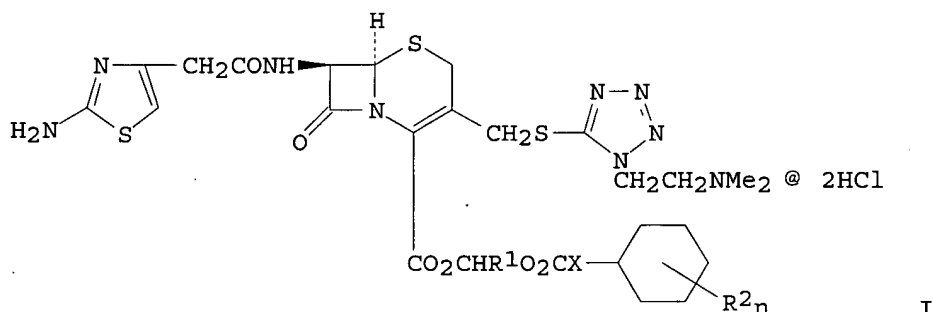
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The bioavailability of L-dopa following rectal administration of a series of short-chain alkyl esters of L-dopa was determined in rats and dogs. The esters were stable ( $>360$  min) to hydrolysis in physiol. buffer. In vitro enzymic hydrolysis of the esters in plasma was species dependent, with the hydrolytic rate being faster in rat plasma ( $t_{1/2} < 5$  min) than dog plasma ( $t_{1/2} = 68-181$  min) or human plasma ( $t_{1/2} = 96-238$  min). In vivo hydrolysis in dogs, as indicated by the L-dopa plasma profile following i.v. administration of the esters, was very rapid (high extravascular esterase activity). Significant L-dopa bioavailability was observed in rats following rectal administration of the Me (46%), Et (14%), iso-Pr (48%), Bu (100%), and 4-hydroxybutyl (13%) esters of L-dopa (rectal L-dopa absorption,  $<5\%$ ). In dogs, significant L-dopa bioavailability was also observed for the Me (28%), iso-Pr (30%), Bu (32%), and 4-hydroxybutyl (34%) esters of L-dopa in the presence of carbidopa. These highly water-soluble ( $>600$  mg/mL) esters of L-dopa are potential candidates for controlled-release rectal delivery systems designed to provide more constant plasma L-dopa levels.

10/511452

L3 ANSWER 23 OF 23 CA COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 106:188379 CA  
TITLE: Orally active 1-(cyclohexyloxycarbonyloxy)  
alkyl ester prodrugs of  
cefotiam  
AUTHOR(S): Nishimura, Tatsuo; Yoshimura, Yoshinobu; Miyake, Akio;  
Yamaoka, Masayoshi; Takanohashi, Kunio; Hamaguchi,  
Naoru; Hirai, Shinichiro; Yashiki, Takatsuka; Numata,  
Mitsuo  
CORPORATE SOURCE: Cent. Res. Div., Takeda Chem. Ind., Ltd., Osaka, 532,  
Japan  
SOURCE: Journal of Antibiotics (1987), 40(1), 81-90  
CODEN: JANTAJ; ISSN: 0021-8820  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
GI



AB Orally active 1-(alkyl substituted-cyclohexyloxycarbonyloxy)alkyl ester prodrugs (I, R1 = H or alkyl, R2n = H or alkyl, n = 0-2, X = O, S, or NH) of cefotiam (II) [61622-34-2] were studied. The syntheses and oral bioavailability (BA) in mice are described. Among them, I (R1 = Pr, R2n = H, X = O) (III) [95761-79-8] gave the highest BA, 93.5%; the ester having a cyclohexyloxy group in the ester moiety gave BAS of >75%, although the BA of the 1-(ethoxycarbonyloxy)ethyl ester [108098-64-2] was only 23.9%. The thia analog of III [108118-39-4] showed a moderate BA, 46%, but the aza analog of III [108118-37-2], did not show the bioavailability of II. The 1-(substituted cyclohexyloxycarbonyloxy)alkyl group was thus a suitable promoiety to improve the oral BA of II. Chiral 1-(alkoxycarbonyloxy)alkyl groups used as the ester moiety, gave an almost 1:1 mixture of diastereoisomeric esters. These were tested as such. However, an experiment in which the separated isomers of the 1-(cyclohexyloxycarbonyloxy)ethyl ester were administered orally confirmed that both diastereoisomers gave identical BAs.

10/511452

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FILE 'CA' ENTERED AT 08:40:05 ON 06 NOV 2006

L1 1 S PRODRUG? AND (SIMPLE ESTER)

FILE 'STNGUIDE' ENTERED AT 08:40:38 ON 06 NOV 2006

FILE 'CA' ENTERED AT 08:42:06 ON 06 NOV 2006

L2 23 S ALKYL ESTER PRODRUG?

L3 23 S L2 NOT L1

=> s l3 and pain

42603 PAIN

L4 0 L3 AND PAIN

=

=> d his

(FILE 'HOME' ENTERED AT 08:39:33 ON 06 NOV 2006)

FILE 'CA' ENTERED AT 08:40:05 ON 06 NOV 2006

L1 1 S PRODRUG? AND (SIMPLE ESTER)

FILE 'STNGUIDE' ENTERED AT 08:40:38 ON 06 NOV 2006

FILE 'CA' ENTERED AT 08:42:06 ON 06 NOV 2006

L2 23 S ALKYL ESTER PRODRUG?

L3 23 S L2 NOT L1

L4 0 S L3 AND PAIN

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Executing the logoff script...

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STN INTERNATIONAL LOGOFF AT 08:50:19 ON 06 NOV 2006